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English translation of the specification of the International Patent Application No. PCT/CH03/00216 "Kneadable and moldable bone-replacement material" in the name of Mathys Medizinaltechnik AG

Kneadable and moldable bone-replacement material

The invention concerns a kneadable and moldable bone-replacement material in accordance with the general term of patent claim 1.

Under current standards of technology it is common practice to use blocks or granulates made from synthetically produced calcium phosphate for re-filling of defective bones. The disadvantages of this material lie in the fact that the blocks must be tailored to the shape of the defective bone they are to be used on as well as in the fact that the time spent in the application of the loose granulates is not at optimum level.

In addition, materials which can be injected are also known. These however consist mainly of spheric particles (small balls). These materials with spheric balls can be injected more easily into the bone because the small balls slide past each other with greater ease. This however is a disadvantage in the case of kneadable and moldable bone-replacement materials, as they are meant to be kneaded rather than injected. Such a material should therefore be cohesive, a requirement which is not met by spheric particles.

In the following text, the term "particle" includes any three-dimensional body, regardless of its dimensions, especially the small parts commonly known as "granulate" or "grains".

This discussion regarding current standards of technology is used only to explain the environment of the invention and does not mean that the standards of technology quoted here were actually published or publicly known at the time of this registration or its priority.

This invention is meant to provide a remedy for this situation. The invention is based on the problem of creating a kneadable bone-replacement material which overcomes the disadvantages listed above, especially the shaping and the time required for application.

The invention solves this task through a kneadable and moldable bone-replacement material which has the characteristics of claim 1.

The advantage of eliminating the danger of transferring diseases due to the absence of possible pathogenic agents such as proteins, germs, viruses or bacteria as compared to bone-replacement materials of natural origin is thus achievable.

Another advantage lies in the fact that it is no longer necessary to transfer the loose ceramic particles laboriously one by one to the desired location of use. Instead, using the kneadable bone-replacement material, the required total quantity of

ceramic particles can be transferred to the location of use quickly and easily. In addition, non-spheric and especially angular particles encourage ceramic resorption and accelerate tissue growth and bone recovery. Compared to materials with nearly spheric particles, the non-spheric and especially the angular particles improve the cohesion of the kneadable material.

"Non-spheric" describes any particle shape which is significantly different from a spheric shape. One variant of the invention uses ceramic particles with an angular shape. "Angular" describes those particles which have individual edges, especially those which are visible with the naked eye, i.e. which are at least 0.1 mm in size.

Compared to round particles, this results in an increase to the particle surface, while the average particle diameter remains the same. This causes the adhesive interaction between the particles and the hydrogel to be increased, guaranteeing the moldability of the bone-replacement material without the need for increasing the quantity of hydrogel used or its concentration.

There is also a special variant whose ceramic particles have a spheric relationship  $S = D_{\max}/D_{\min}$  between the largest diameter  $D_{\max}$  and the smallest diameter  $D_{\min}$  of the individual particles, which is larger than 1.2 and preferably larger than 1.5. The value of  $S$  should be larger than 3 and preferably larger than 5.

At least 60% and typically at least 80% of the ceramic particles should be of a non-spheric shape.

The pore size of the ceramic particles should be between 1 and 500 micrometers. The ceramic particles typically have a share of macropores which are between 100 and 500 micrometers in size and a share of micropores which are between 1 and 100 micrometers in size. This guarantees optimum pore size distribution and the growth of autogenous tissue through the pores. The porosity of the ceramic particles should be between 60 and 90 percent. This ensures that autogenous tissue is able to grow through a larger volume share of ceramic particles.

The bulk density of the ceramic particles should be between 0.2 g/ccm and 2.0 g/ccm. It is typically between 0.6 g/ccm and 1.0 g/ccm and preferably between 0.7 g/ccm and 0.9 g/ccm. In one variant, the bulk density of the ceramic particles is between 1.0 g/ccm and 2.0 g/ccm, preferably between 0.2 g/ccm and 1.8 g/ccm.

The advantage of the higher bulk density ranges is a higher mechanical stability, the disadvantages however are slower resorption and slower bone re-growth. The advantages of lower bulk density ranges are faster resorption and improved bone re-growth.

The jarring density of the ceramic particles should be between 0.5 g/ccm and 2.5 g/ccm, preferably between 0.7 g/ccm and 1.1 g/ccm or between 1.1 g/ccm and 2.5 g/ccm.

The apparent density of the ceramic particles can be further increased by using ceramic particles of different grain sizes. The interstitial space (dead volume) between the larger particles is filled by smaller particles. The intercalating of the ceramic particles further improves the mechanical characteristics of the kneading material.

The average diameter of the ceramic particles should be between 100 and 250 micrometers. The advantage of this is the fact that the bone-replacement material is compact. In addition, the risk of irritation within the tissue surrounding the particles is practically non-existent, if the diameter of the particles is not smaller than 100 micrometers.

The average diameter of the ceramic particles can also be between 150 and 500 micrometers or between 0.5 and 5.6 mm for more efficient filling of medium-sized and larger defects.

It is also possible to mix ceramic particles with an average diameter between 100 and 250 micrometers and particles with an average diameter between 250 and 500 micrometers or an average diameter between 0.5 and 5.6 mm. This has the advantage that it guarantees the compactness of the bone-replacement material. The interstitial pore volume (pore dead volume) which results from the use of large-grain material can thus be reduced to a minimum. It is also possible to affect the degradation period of the hardened bone-replacement material through the use of ceramic particles of various sizes.

The ceramic particles should consist of a calcium-phosphate, typically beta-tricalcium-phosphate. This means that a ceramic is being used whose stoichiometric makeup is very close to that of the human bone. In addition, the degradation period of beta-tricalcium-phosphate is neither too fast nor too slow, preventing the development of hollow spaces or implant residue during degradation.

The ceramic particles consisting of calcium-phosphate have the advantage of possessing a molar Ca/P relationship in the range between 1.0 and 2.0 and preferably in the range between 1.45 and 1.52. The range between 1.45 and 1.49 is preferred.

The calcium-phosphate can be selected from the following group:

Dicalcium-phosphate-dihydrate ( $\text{CaHPO}_4 \times 2 \text{H}_2\text{O}$ ), dicalcium-phosphate ( $\text{CaHPO}_4$ ), alpha-tricalcium-phosphate ( $\alpha\text{-Ca}_3(\text{PO}_4)_2$ ), beta-tricalcium-phosphate ( $\beta\text{-Ca}_3(\text{PO}_4)_2$ ), calcium-deficient hydro-xyapatite ( $\text{Ca}_9(\text{PO}_4)_5(\text{HPO}_4)\text{OH}$ ), hydro-xyapatite ( $\text{Ca}_{10}(\text{PO}_4)_6\text{OH}$ ), carbonated apatite ( $\text{Ca}_{10}(\text{PO}_4)_3(\text{CO}_3)_3(\text{OH})_2$ ), fluoride-apatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{F},\text{OH})_2$ ), chloride-apatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{Cl},\text{OH})_2$ ), whitlockite ( $((\text{Ca},\text{Mg})_3(\text{PO}_4)_2)$ ), tetracalcium-phosphate ( $\text{Ca}_4(\text{PO}_4)_2\text{O}$ ), oxyapatite ( $\text{Ca}_{10}(\text{PO}_4)_6\text{O}$ ), beta-calcium-pyrophosphate ( $\beta\text{-Ca}_2(\text{P}_2\text{O}_7)$ ), alpha-calcium-pyrophosphate, gamma-calcium-pyrophosphate, octo-calcium-phosphate ( $\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \times 5 \text{H}_2\text{O}$ ).

The ceramic particles may also consist of a mixture of different calcium-phosphates. The advantage of such a mixture lies in the control of the resorption period. Due to the differing resorption behaviours of the mixture components, faster bone growth into the cavities of components with faster resorption times can be facilitated.

The ceramic particles can also consist of calcium-sulfate or calcium-carbonate.

For a special variant, the ceramic particles can be selected from the following group: alpha-calcium-sulfate-hemihydrate, beta-calcium-sulfate-hemihydrate, calcium-sulfate-dihydrate.

For another variant, the ceramic particles may consist of a mixture of different calcium-phosphates, calcium-sulfates and/or calcium-carbonates. The advantage of such a mixture lies in the control of the resorption period. Due to the differing resorption behaviours of the mixture components, faster bone growth into the cavities of components with faster resorption times can be facilitated.

The non-spheric particles can be generated by breaking or grinding of larger porous blocks of the desired material. The desired particle sizes can be achieved by using appropriate sieves.

For a special variant, the bone-replacement material may also contain metallic or semi-metallic ion shares. The advantages of such ion contents are their impact upon the resorption behaviour of the ceramic, allowing optimum replacement of the mineral composition of the bone.

The matrix which the hydrogel consists of or the substance which may be swelled into a hydrogel may be selected from the following substance groups:

- a) fully synthetic substances;
- b) natural biological substances of plant origin; and/or
- c) biotechnologically generated substances.

The hydrogel or the substance which can be swelled into a hydrogel can also consist of a mixture of fully synthetic, natural biological or biotechnologically generated substances.

A hydrogel is present when a solid substance is hydrated via a liquid phase, changing and increasing the viscosity of the liquid phase, i.e. jellying or coagulating the liquid phase.

The hydrogel matrix can consist of oligomeric or polymeric shares or of a combination of the two. Pharmaco-additives may be mixed into the bone-replacement material as required. The jellying liquid for the hydrogel can be water, especially deionised water and/or an organic, body-compatible solvent.

For a special variant, the hydrogel or the substance which can be swelled into a hydrogel contains one of the following components: a) polyamino-acids or their derivatives, preferably polylysine or gelatin; b) polysaccharides and their derivatives, preferably glycosaminoglycane or alginate; c) polylipides, fatty acids and their derivatives; d) nucleotides and their derivatives; or a combination of the components as listed in a) through d).

For another variant, the hydrogel or the substance which can be swelled into a hydrogel contains one of the following synthetic components: a) polymethylenoxide or its derivatives; b) polyethylene, polyethylenoxide or their derivatives; c) polypropylene, polypropylenoxide or their derivatives; d) polyacrylate or its derivatives; or a combination of the components as listed in a) through d).

For a special variant, the hydrogel or the substance which can be swelled into a hydrogel is either a glycosaminoglycane or a proteoglycane or a mixture of those two substances. The glycosaminoglycane can be a hyaluron-acid, chondroitinsulfate, dermatansulfate, heparansulfate, heparine or keratansulfate.

The concentration of the ready-to-use, hydrated hydrogel or the ready-to-use, hydrated substance which can be swelled into a hydrogel should be between 0.1% and 20.0%.

The molecular weight of the hydrogel or the substance which can be swelled into a hydrogel should exceed 300'000 Dalton and is preferred to be above 500'000 Dalton. For another variant, the molecular weight of the hydrogel or the substance which can be swelled into a hydrogel exceeds 1'000'000 Dalton and is preferred to be above 1'500'000 Dalton. A larger molecular weight means that a smaller amount of hydrogel is required to achieve a certain level of viscosity. Therefore a large number of viscous jellies can be created with a relatively small hydrogen content.

For a special variant, the hydrogel is a liquid solution of a hyaluronate. The hyaluron-acid consists of glucoron-acid and acetylglucosamine which create the disaccharide hyaluron-acid. The hyaluron-acid has a fibrous, non-branced molecular structure and therefore results in highly viscous liquid solutions.

The liquid solution of the hydrogel typically contains less than 99% water and preferably less than 98% water. In special cases, the liquid solution may contain less than 96.5% water and preferably less than 95% water. Such concentrations have the advantage of guaranteeing the excellent moldability of the bone-replacement material.

The molecular weight of the hyaluron-acid used should be larger than  $1.5 \times 10^6$  Dalton. For a special variant, the molecular weight of the hyaluron-acid used is between  $0.5 \times 10^6$  and  $1.0 \times 10^6$  Dalton.

For another variant, the molecular weight of the hyaluron-acid used is smaller than  $1 \times 10^6$  Dalton and preferably smaller than  $0.5 \times 10^6$  Dalton.

For a special variant, the specific gravity of the calcium-containing, porous ceramic particles is between 0.5 and 1.0 g/ccm.

For another variant, the weight relationship A/B between the hydrated hydrogel and the calcium-containing ceramic particles is larger than 0.2 and preferably between 0.2 and 0.5.

For other variants, the weight relationship A/B is between 0.5 and 0.9 or between 0.9 and 1.3 or between 1.3 and 2.0 or between 2 and 5 or larger than 5.

The advantages of these different ranges for the weight relationship of A/B lie in the different kneadabilities and resorption periods. A high content of substance A makes the material more kneadable, but increases resorption; a high level of substance B makes the material less kneadable, but reduces the rate of resorption.

The invention and further developments of the invention are explained in more detail in the following application examples.

#### Example 1

1.2 g of porous and angular granulate of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 500 micrometers and a sphericity degree of  $S = 3.1$  were mixed with 2.0 g of a 5% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 500 kD. The resulting kneadable material was highly

suitable as a plastic bone-replacement material. It can be kneaded by hand as desired, molded into the desired shape and placed directly into the bone defect to be filled. The moldability allows optimum filling of bone defects.

#### Example 2

A mixture of 0.6 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 100 micrometers and a sphericity degree of  $S = 2.9$  and 0.6 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 500 micron and a sphericity of  $S = 2.7$  was mixed with 2.0 g of a 5% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 900 kD. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 3

A mixture of 0.3 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 100 micrometers and a sphericity degree of  $S = 2.4$  and 0.3 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 500 micron and a sphericity of  $S = 2.3$  was mixed with 1.0 g of a 10% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 900 kD. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 4

A mixture of 0.3 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 100 micrometers and a sphericity degree of  $S = 1.8$  and 0.3 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with an approximate size of 500 micron and a sphericity of  $S = 2.7$  was mixed with 50 mg of biotechnologically generated natrium-hyaluronate with a molecular weight of 900 kD. Then 0.9 g of deionised water were added and thoroughly mixed for 10 minutes. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 5

A mixture of 1.65 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.65 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 3.0 g of a sterile, liquid 6% solution of natrium-hyaluronate (molecular weight of the natrium-hyaluronate = 900 kD) under sterile conditions using a spatula. After 30 minutes, the material was placed into a sterile, tube-shaped container. This sterile kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 6

A mixture of 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 2.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP)

with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 3.0 g of a sterile, liquid 8% chitosane solution under sterile conditions using a spatula. After 30 minutes, the material was placed into a sterile, syringe-like container. The resulting sterile kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 7

A mixture of 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 3.0 g of a sterile, liquid 5% solution of rhCollagen under sterile conditions using a spatula. The resulting sterile kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 8

A mixture of 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 2.5 g of a liquid 5% solution of natrium-alginate. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 9

3.0 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity degree of  $S = 2.9$  were mixed with 2.5 g of a liquid 6.5% polyethyleneglycol solution (MG = 35 kD) using a spatula. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 10

3.0 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity degree of  $S = 2.9$  were mixed with 2.0 g of a liquid 4% polyethylenoxide solution (MG = 511 kD) using a spatula. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 11

3.0 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity degree of  $S = 2.5$  were mixed with 2.2 g of a liquid 10% solution of hydroxymethyl-cellulose using a spatula. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 12

A mixture of 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 2.5 g of a liquid 7% solution of Ploronic 407. Ploronic 407 is a substance with a chemical makeup of  $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$  with  $a = 101$  and  $b = 56$ . The resulting sterile kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 13

A mixture of 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  was mixed with 2.5 g of a liquid solution consisting of 0.18 g of natrium-hyaluronate (MG = 1.4 million Dalton) and 0.09 g of polyethylenoxide (MG = 511 kD). The resulting sterile kneadable material was highly suitable as a plastic bone-replacement material.

#### Example 14

0.2 g of natrium-malginate (MG = 50-500 kD) and 1.0 of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.5$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.9$  were mixed thoroughly when dry. 2.0 g of deposited water were then stirred into this mixture. This resulted in a kneadable material which was able to be used as a plastic bone-replacement material.

#### Example 15

0.18 g of natrium-hyaluronate (MG = 1.1 – 1.3 million Dalton) and 1.0 of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.9$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.5$  were mixed thoroughly when dry. 0.5 ml of platelet-rich plasma and 1.5 ml of sterile deionised water were then stirred into this mixture. After thorough mixing, this resulted in an excellent plastic kneadable material which was able to be used as a plastic bone-replacement material.

#### Example 16

0.18 g of natrium-hyaluronate (MG = 1.1 – 1.3 million Dalton) and 1.0 of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 500 to 700 micrometers and a sphericity degree of  $S = 2.9$  and 1.5 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta$ -TCP) with a grain size of 125 to 500 micrometers and a sphericity of  $S = 2.5$  were mixed thoroughly when dry. 2 ml of fresh blood were then stirred into this mixture. After thorough mixing, this resulted in an excellent plastic kneadable material which was able to be used as a plastic bone-replacement material.



Example 17

A mixture of 0.6 g of porous and angular granulates of dicalcium-phosphate-dihydrate ( $\text{CaHPO}_4 \times 2 \text{H}_2\text{O}$ ) with an approximate size of 100 micrometers and a sphericity degree of  $S = 2.9$  and 0.6 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta\text{-TCP}$ ) with an approximate grain size of 500 micrometers and a sphericity of  $S = 2.7$  was mixed with 2.0 g of a 5% liquid solution of biotechnologically generated natrium hyaluronate with a molecular weight of 900 kD. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

Example 18

A mixture of 0.6 g of porous and angular granulates of dicalcium-phosphate ( $\text{CaHPO}_4$ ) with an approximate size of 100 micrometers and a sphericity degree of  $S = 1.5$  and 0.6 g of porous and angular granulates of dicalcium-phosphate ( $\text{CaHPO}_4$ ) with an approximate size of 500 micrometers and a sphericity of  $S = 2.7$  was mixed with 2.0 g of a 5% liquid solution of biotechnologically generated natrium hyaluronate with a molecular weight of 900 kD. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

Example 19

A mixture of 0.3 g of porous and angular granulates of calcium-deficient hydroxylapatite (CDHA;  $\text{Ca}_9(\text{PO}_4)_5(\text{HPO}_4)\text{OH}$ ) with a specific surface of 55  $\text{sqm/g}$ , an approximate size of 125 micrometers and a sphericity degree of  $S = 1.8$  and 0.3 g of porous and angular granulates of calcium-deficient hydroxylapatite (CDHA;  $\text{Ca}_9(\text{PO}_4)_5(\text{HPO}_4)\text{OH}$ ) with a specific surface of 55  $\text{sqm/g}$ , an approximate size of 500 micrometers and a sphericity of  $S = 2.3$  was mixed with 2.7 g of a 10% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 1.2 million Dalton. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

Example 20

A mixture of 0.3 g of porous and angular granulates of calcium-deficient hydroxylapatite (CDHA;  $\text{Ca}_9(\text{PO}_4)_5(\text{HPO}_4)\text{OH}$ ) with a specific surface of 102  $\text{sqm/g}$ , an approximate size of 125 micrometers and a sphericity degree of  $S = 1.8$  and 0.3 g of porous and angular granulates of calcium-deficient hydroxylapatite (CDHA;  $\text{Ca}_9(\text{PO}_4)_5(\text{HPO}_4)\text{OH}$ ) with a specific surface of 102  $\text{sqm/g}$ , an approximate size of 500 micrometers and a sphericity of  $S = 2.3$  was mixed with 2.7 g of a 10% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 1.2 million Dalton. The resulting kneadable material was highly suitable as a plastic bone-replacement material.

Example 21

A mixture of 0.3 g of porous and angular granulates of calciumsulfate-hemihydrate with an approximate size of 125 micrometers and a sphericity degree of  $S = 1.8$  and 0.3 g of porous and angular granulates of beta-tricalcium-phosphate ( $\beta\text{-TCP}$ ) with an approximate grain size of 500 micrometers and a sphericity of  $S = 2.3$  was mixed

with 2.7 g of a 7% liquid solution of biotechnologically generated natrium-hyaluronate with a molecular weight of 1.4 million Dalton. The resulting kneadable material was highly suitable as a plastic bone-replacement material.